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TITLE: Evaluation of Feasibility for a Case-Control Study of Adrenal Androgen Production in Postmenopausal Women With Breast Cancer

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Postmenopausal women with elevated serum estrogens and androgens are at an increased risk of breast cancer [I]. Dehydroepiandrosterone sulfate (DHEAS) is secreted only by the adrenals, and elevated serum DHEAS levels in postmenopausal women who develop breast cancer suggest increased adrenal androgen production. The objective of this pilot study was to evaluate variation in responsiveness of adrenal hormones to ACTH stimulation in healthy postmenopausal women. We also evaluated variation in natural killer cell cytotoxicity in response to ACTH. ACTH stimulation was accomplished by infusing a physiologic dose of synthetic ACTH over one hour following overnight adrenal suppression with dexamethasone. Results indicate considerable variation in response of serum progesterone, cortisol, DHEA, and androstenedione following ACTH stimulation. Other hormones measured and natural killer cell cytotoxictiy did not change significantly after ACTH. Future analyses will attempt to identify determinants of variation in response of progesterone, cortisol and adrenal androgens to ACTH stimulation.

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# Table of Contents


Front Cover ..... 1

Standard Form 298 ..... 2

Table of Contents ..... 3

Introduction ..... 4

Body ..... 4

Key Research Accomplishments ..... 7

Reportable Outcomes ..... 7

Conclusions ..... 8

References ..... 8

Appendices ..... 10

## Introduction

Postmenopausal women with elevated serum estrogens and androgens are at an increased risk of breast cancer [1]. Dehydroepiandrosterone sulfate (DHEAS) is secreted only by the adrenals, and elevated serum DHEAS levels in postmenopausal women who develop breast cancer suggest increased adrenal androgen production. The original objective of this pilot study was to evaluate the feasibility of conducting a case-control study that uses adrenocorticotropic hormone (ACTH) stimulation tests to determine if postmenopausal women who develop breast cancer secrete more adrenal androgens, which are converted to estrogens in peripheral tissues, in response to ACTH stimulation compared to unaffected women. However, the study as originally planned was not feasible because women with a history of breast cancer were unwilling to undergo an ACTH stimulation test that was done strictly for research purposes. Therefore, in consultation with our Army Contracting Officer Representative, we modified the scope of work to evaluate variation in responsiveness of adrenal hormones to ACTH stimulation in healthy postmenopausal women. We also evaluated variation in natural killer cell cytotoxicity in response to ACTH stimulation.

## Body

### Methods

The study took place at the Fox Chase Cancer Center and included 7 women living in the Philadelphia area who were identified via flyers and newspaper advertisements. To be eligible, women had to be 50-70 years old and healthy, postmenopausal (defined as one year since last menses if menopause occurred naturally or have a basal serum follicle stimulating hormone (FSH) > 40 ng/ml if menopause was surgical and the participant was <60 years old), have at least one intact ovary, have had a mammogram within the past 2 years and have no evidence of breast pathology, be in the $90^{th}$ – $130^{th}$ percentile ideal weight for height, have no history of cancer other than non-melanoma skin cancer, not have a history of hypersensitivity to dexamethasone or ACTH, not have a systemic fungal infection, and not be taking any medications that could interfere with the study.

The study involved participation in two clinic visits. Both visits were scheduled between 8:00 am and 10:00 am during a 2 week period. Participants were instructed to fast for 10 hours before each visit. At the first visit, final determination of eligibility was determined and a blood sample was collected for measurement of basal hormone concentrations. At the conclusion of the first visit, eligible participants were given two .5 mg Decadron tablets to take with water before bed the night before the second visit. This is a standard dose for overnight dexamethasone suppression testing [2]. At the second visit, a physiologic dose (320 ng/1.5$m^2$·h) of synthetic ACTH (1-24, Cortrosyn) was infused over one hour through an IV. This dose was chosen because it is the minimal dose necessary to achieve a physiologic response in adrenal androgen production [3]. Blood was collected through a second IV at 15 minutes and 1 minute before ACTH administration for measurement of Dexamethasone suppressed hormone concentrations, and at 15, 30 and 60 minutes after start of ACTH administration to detect ACTH stimulated concentrations.

All hormones, except ACTH, and cytokines were measured in serum. Blood was allowed to sit at room temperature for a minimum of 60 minutes before serum was separated, aliquoted into cryovials and stored at -80°. ACTH was measured in plasma (EDTA) that was collected on ice, separated within one hour of collection, aliquoted into cryovials and stored at -80°. NK cell activity was measured in fresh whole blood that was collected at room temperature.

All hormone assays were performed at the Reproductive Endocrinology Laboratory, University of Southern California under the direction of Dr. Frank Stanczyk. Progesterone, androstenedione, dehydroepiandrosterone, testosterone, estrone and estradiol were quantified by validated, previously described radioimmunoassays (RIAs) [4-6]. Prior to RIA, steroids were extracted from serum with hexane:ethyl acetate (3:2). The steroids were then separated by Celite column partition chromatography using either trimethylpentane, toluene in trimethylpentane, or ethyl acetate in trimethylpentane. ACTH and leptin were measured by direct RIAs using kits obtained from Diagnostic Systems Laboratory (Webster, TX). DHEAS, cortisol, and sex hormone binding globulin (SHBG) were quantified by direct chemiluminescent immunoassays using the Immulite analyzer (Diagnostic Products Corporation, Los Angeles, CA). Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF$\alpha$) levels were determined by direct ELISAs using kits obtained from R&D (Minneapolis, MN).

All the immunoassay methods were shown to be reliable. Serum was used for measurement of all analytes except ACTH, which was quantified in plasma. Specificity was achieved by use of highly specific antisera and/or use of organic solvent extraction and chromatographic steps prior to quantification of the analytes. Assay accuracy was established by demonstrating parallelism between measured concentrations of a serially diluted analyte in serum with the corresponding standard curve. Intraassay and interassay coefficients of variation ranged from 4 to 8% and 8 to 13%, respectively.

Natural killer (NK) cytotoxicity was measured at the Immunology Laboratory at Children's Hospital of Philadelphia under the direction of Dr. Steven Douglas. NK cytotoxicity was measured by release of 51Cr from isotopically-labeled target cells and expressed as lytic units.

Preliminary analyses presented in this report included graphical displays of data, estimation of means and standard deviations, and tests for differences in analyte levels at the various time points by repeated measures analysis of variance (ANOVA) implemented by SAS Proc Mixed. More detailed analyses are planned prior to publication.

## Results

Basal, dexamethasone suppressed, and ACTH stimulated hormone concentrations for each participant are plotted in Figure 1. ACTH levels fell from a mean of 39.92 pg/ml to 25.42 pg/ml following dexamethasone suppression ($p=.08$) and increased again to 36.64 pg/ml following ACTH stimulation ($p=.07$). However, there was considerable variation in the pattern of response among participants.

Cortisol concentrations at the five time points differed considerably ($F_{4/6}=93.76$, $p<.0001$). Following dexamethasone suppression, serum cortisol levels fell from a mean of 8.16 μg/dl to

.59 μg/dl ($p<.0001$). Serum cortisol levels increased following ACTH stimulation so that mean concentrations at 30 minutes (8.91 μg/dl) and 60 minutes (12.87 μg/dl) post ACTH stimulation were significantly ($p<.05$) higher than pre-stimulation levels. Whereas the cortisol response to dexamethasone suppression was similar for all participants, there was considerable variation in response to ACTH stimulation. One participant exhibited an almost immediate dramatic increase in serum cortisol level, whereas others exhibited a more gradual increase and some showed only a small change following ACTH stimulation.

The overall F-test for differences in DHEA also was significant ($F_{4/6}=12.74$, $p=.004$). Similar to cortisol, DHEA concentrations fell significantly ($p=.003$) following dexamethasone suppression from a mean of 2.22 ng/ml to 0.94 ng/ml. DHEA rose significantly following ACTH stimulation so that by 30 minutes post-stimulation, DHEA levels averaged 1.97 ng/ml ($p=.05$ for comparison to pre-stimulation levels) and remained elevated at 60 minutes when the mean was 2.42 ng/ml ($p=.02$ for comparison to pre-stimulation levels). Patterns of individual DHEA responses to dexamethasone suppression and ACTH stimulation generally were similar to patterns for cortisol. Although DHEAS levels did not change following dexamethasone suppression ($p=.98$), this was anticipated because of the large pool of circulating DHEAS. We did not measure DHEAS post ACTH stimulation for this reason.

The androstenedione response to dexamethasone suppression and ACTH stimulation was similar to that observed for cortisol and DHEA. Androstenedione concentrations fell significantly ($p=.0007$) following dexamethasone suppression from a mean of .59 ng/ml to .23 ng/ml. Androstenedione increased significantly following ACTH stimulation so that by 30 minutes post-stimulation androstenedione concentrations averaged .54 ng/ml ($p=.03$ for comparison to pre-stimulation levels) and this level was maintained at 60 minutes. The pattern of individual androstenedione responses was also generally similar to cortisol and DHEA.

Progesterone concentrations exhibited a similar pattern to cortisol and the adrenal androgens. In particular, one participant exhibited an early dramatic increase in progesterone levels following ACTH stimulation. Serum progesterone levels decreased significantly ($p=.02$) from a mean of 115.52 pg/ml before dexamethasone to a mean of 55.36 pg/ml afterward. However, most participants exhibited only modest changes in progesterone following stimulation and mean concentrations of progesterone in serum collected after ACTH stimulation did not differ significantly from pre-stimulation levels.

Testosterone concentrations fell significantly ($p=.002$) from a mean of 27.82 ng/dl to 16.76 ng/dl following dexamethasone suppression and increased gradually after ACTH stimulation so that by 60 minutes post-stimulation, testosterone levels averaged 21.50 ng/dl, which was significantly higher than pre-stimulation levels ($p=.005$). Estrone also fell significantly ($p=.05$) following dexamethasone suppression from a mean of 44.57 pg/ml to 28.40 pg/ml and increased gradually following ACTH stimulation. At 60 minutes post-stimulation estrone levels averaged 33.90 pg/ml ($p=.07$ for comparison to pre-stimulation levels). Estradiol did not change following dexamethasone suppression or ACTH stimulation, and SHBG was unchanged following dexamethasone suppression.

NK cell activity also did not change following dexamethasone suppression or ACTH stimulation (Figure 2).

Further analyses are planned to evaluate effects of age and race on results as well as whether results varied by serum TNF-α, IL-6, and leptin concentrations (Figure 3).

**Key Research Accomplishments**:

- The goal of this pilot study was to determine the feasibility of conducting a case-control study to compare adrenal response to dexamethasone suppression and ACTH stimulation in breast cancer patients vs. healthy controls. We demonstrated that such a study is not feasible at our institution because it was not possible to recruit breast cancer patients and it was very difficult to recruit healthy controls.

- The major reason women gave for not being interested in participating in the study was they did not want to take any drugs. In future research, we plan to use a behavioral approach to stimulating the adrenals.

- The research team gained experience working together. The PI and a co-investigator (unfunded) have subsequently submitted several grants together.

**Reportable Outcomes**

- We plan to write a manuscript reporting our results. Some findings salient to hormonal determinants of breast cancer are:

  - Hormonal responses to dexamethasone suppression and ACTH stimulation vary across women. Further analyses are planned to attempt to identify the reasons for these differences including age, weight and cytokine levels.

  - One woman exhibited a rapid and dramatic hormonal response to ACTH stimulation. Because progesterone was elevated in addition to DHEA and cortisol, this suggests the possibility of a polymorphism in the ACTH receptor or steroid acute regulatory protein (STAR).

  - Basal hormone levels do not always predict adrenal response to stimulation. For example, the woman with the highest progesterone concentration following ACTH stimulation had the lowest basal concentration and the woman with the lowest progesterone concentration following stimulation had an average basal concentration.

- Based on experience conducting the research for this study, we submitted an R03 to NIH that used a behavioral approach to stimulating the adrenals. Our score was not in the fundable range. We have not yet seen the pink sheets, but results of this study may be useful in responding to reviewers comments.

- The knowledge we gained through this project and other sources about adrenal physiology was used in developing a contract proposal to identify genetic and environmental factors that contribute to breast cancer risk in postmenopausal women. We have not yet learned whether this study will be funded.

**Conclusions**

There is considerable between person variation in adrenal response to dexamethasone suppression and ACTH stimulation. Because postmenopausal women who develop breast cancer have higher adrenal androgen concentrations (DHEA, DHEAS, and androstenedione) compared to healthy women, these differences could be important determinants of breast cancer risk. Regrettably, we were unable to recruit breast cancer patients to compare responsivity as originally planned. However, it may be feasible to identify genetic variants that influence adrenal responsivity and then determine if the distribution of these variants differs by breast cancer status. We plan to continue to pursue this line of research and the data collected in this pilot study will be used to support future grant applications.

**References:**


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**List of Personnel**

- Dorgan, Joanne F. - Principal Investigator
- Fang, Carolyn – Co-Investigator
- Weil, Susan – Co-Investigator
- Godwin, Andrew – Co-Investigator

- Moore, Dirk – Co-Investigator
- Stanczyk, Frank – Co-Investigator
- Douglas, Steven – Co-Investigator

**Appendices**

Email from Wendy Baker, USAMRAA approving request for change in work statement.

**Supporting Data**

Figure 1. Hormonal Responses to Dexamethasone Suppression and ACTH Stimulation in Postmenopausal Women

> Legend: Hormone concentrations at visit 1 (BL) and at visit 2 following dexamethasone suppression at 1 minute before ACTH stimulation (-1 min), and at 15, 30 and 60 minutes following ACTH stimulation in 7 healthy postmenopausal women. Data for each woman is shown in a different color.

Figure 2. Natural Killer Cell Cytotoxicity Following Dexamethasone Suppression and ACTH Stimulation in Postmenopausal Women

> Legend: Natural Killer Cell Cytotoxicity at visit 1 (BL) and at visit 2 following dexamethasone suppression at 1 minute before ACTH stimulation (-1 min), and at 30 minutes following ACTH stimulation in 7 healthy postmenopausal women. Data for each woman is shown in a different color.

Figure 3. Serum TNF-α, IL-6 and Leptin Concentrations in Postmenopausal Women

> Legend: TNF-α, IL-6 and Leptin Concentrations at visit 2 before ACTH stimulation. Data for each woman is shown in a different color.

From: Baker, Wendy A Ms USAMRAA [wendy.cockerham@us.army.mil]
Sent: Thursday, February 16, 2006 1:22 PM
To: Dorgan, Joanne F.
Cc: Sells, Mary Ann; Emgushov, Lisa; Moore, Katherine H Dr USAMRMC
Subject: RE: DAMD 170110237

Dr. Dorgan~

The GOR has now approved your request to utilize the remaining funds on this grant for the collection of pilot data on serum levels of hormones in the adrenal steriodogenesis pathway to determine where in the pathway healthy postmenopausal women with higher basal levels of testosterone and estradiol differ from healthy postmenopausal women who have lower basal levels of these hormones. This approval is granted on the basis that it does not require additional sampling and the existing consent forms allow for additional analyses of the samples. This is now approved for implementation.

Regards,

Wendy Baker
Contract Specialist

-----Original Message-----
From: Dorgan, Joanne F. [mailto:JF_Dorgan@fccc.edu]
Sent: Wednesday, December 21, 2005 2:13 PM
To: 'kathy.moore@us.army.mil'
Cc: Baker, Wendy A Ms USAMRAA; Sells, Mary Ann; Emgushov, Lisa
Subject: FW: DAMD 170110237

Dear Dr. Moore,

This is to follow-up on our telephone conversation earlier today about my DOD Idea Award (DAMD 170110237). The proposed analysis of additional biomarkers would not require recruiting additional participants nor would it require collection of additional specimens. The analyses would be done using samples that we have already collected from participants and stored.
The informed consent document states that the samples may be used for other purposes and that the participant will not receive notice of any future use.
I hope that this clarifies the issues involved. Please inform me how I

should proceed.

Thank you for your assistance,
Joanne Dorgan

----Original Message-----
From: Baker, Wendy A Ms USAMRAA [mailto:wendy.cockerham@us.army.mil]
Sent: Tuesday, December 20, 2005 4:21 PM
To: Dorgan, Joanne F.
Cc: Sells, Mary Ann; Emgushov, Lisa
Subject: RE: DAMD 170110237

Hi Joanne,

I just retrieved your voice message from Friday regarding the emails I sent to you. I think it would be best if you would contact Dr. Kathy Moore, GOR, directly since the discussion will be of a scientific nature. Her phone number is (301) 619-6882. Please let me know what the verdict is. Happy holidays!

Wendy

-----Original Message-----
From: Baker, Wendy A Ms USAMRAA
Sent: Thursday, December 15, 2005 1:01 PM
To: 'Dorgan, Joanne F.'
Cc: Sells, Mary Ann; Emgushov, Lisa
Subject: RE: DAMD 170110237

Joanne,

Dr. Moore's concerns are the same as with 01-1-0236. If you are able to do this new analysis on samples collected as part of your currently approved protocol, then this would be a good use of the funding. If a new protocol is needed, the GOR does not recommend approval of the revision to the project. Please advise.

Regards,

Wendy Baker
Contract Specialist

-----Original Message-----
From: Dorgan, Joanne F. [mailto:JF_Dorgan@fccc.edu]
Sent: Wednesday, December 07, 2005 4:55 PM
To: Baker, Wendy A Ms USAMRAA
Cc: Sells, Mary Ann; Emgushov, Lisa
Subject: DAMD 170110237

Dear Wendy,

I received a DOD Idea Award in 2001 for a proposal entitled 'Evaluation of Feasibility for a Case-Control Study of Adrenal Androgen Production in Postmenopausal Women with Breast Cancer' (DAMD 170110237). The objective of that study was to evaluate the feasibility of conducting a case-control study that uses adrenocorticotropic hormone (ACTH) stimulation tests to determine if postmenopausal women who develop breast cancer secrete more adrenal androgens, which are converted to estrogens in peripheral tissues, in response to ACTH stimulation compared to unaffected women. The pilot study involved recruiting 8 postmenopausal women with breast cancer, 8 spouses of men with cancer, and 8 healthy control women. Because of IRB concerns, the study was conducted in phases; the first phase included only healthy control women, the second phase included spouses of men with cancer, and the third phase was to include women with a history of breast cancer.
We completed the first phase and the Data and Safety Monitoring Board at FCCC and the DOD IRB approved continuing to the second phase. However, although we have advertised widely, we have not had any success in recruiting for the second phase and have not had any success lining up women for the third phase. Thus, we have concluded that a full-scale study is not feasible.

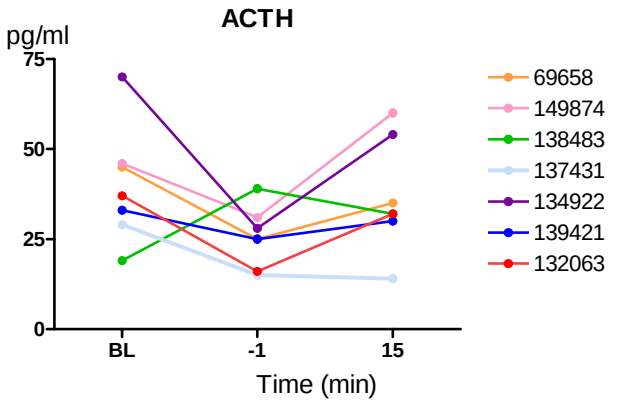
Some funds still remain in the budget and we propose that they be used for an analysis that is different from but related to our previous project.
Specifically, we propose that the remaining funds be used to collect pilot data on serum levels of hormones in the adrenal steroidogenesis pathway to determine where in the pathway healthy postmenopausal women with higher basal levels of testosterone and estradiol differ from healthy postmenopausal women who have lower basal levels of these hormones. Since adrenal androgen secretion is dynamic, differences in stimulated as well as unstimulated levels could be informative. These data would be used to support a prospective study of basal levels of serum hormones in the steroidogenesis pathway with breast cancer risk in postmenopausal women using stored serum that was collected previously

under a different mechanism.

Please let me know if you agree with this suggestion and how I should proceed.

Thank you for your assistance,
Joanne Dorgan

## Figure 1. Hormonal Responses to Dexamethasone Suppression and ACTH Stimulation in Postmenopausal Women

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|---|---|---|---|
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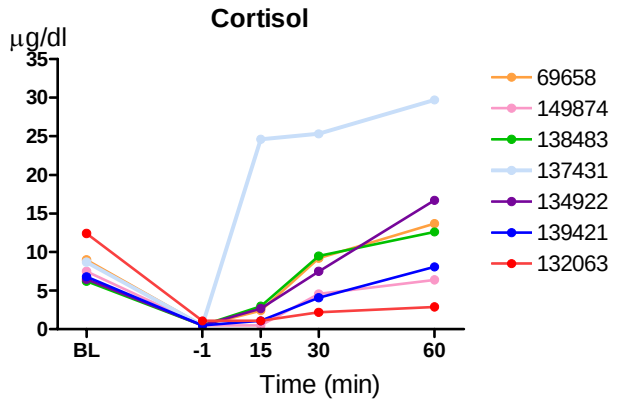
| Std Dev: | 16.45 | 8.35 | 15.78 |




| | | | | | |
|---|---|---|---|---|---|
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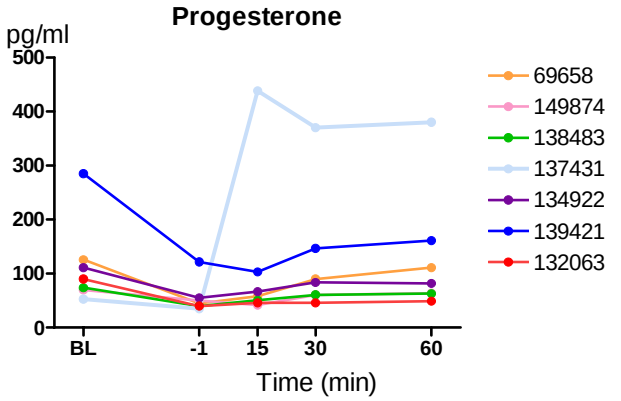
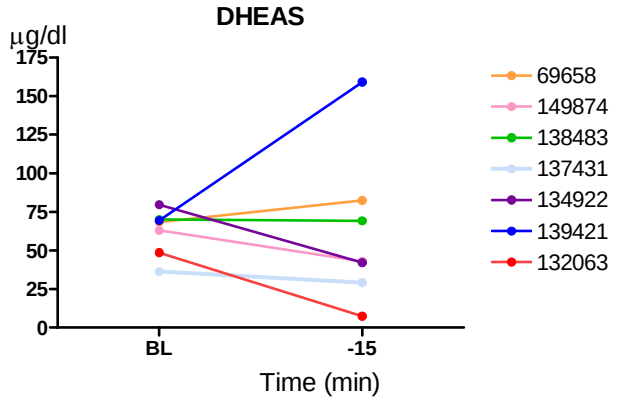
| Std Dev: | 2.15 | 0.23 | 8.67 | 7.72 | 8.78 |




| | | | | | |
|---|---|---|---|---|---|
| Mean: | 115.52 | 55.36 | 115.10 | 122.85 | 130.00 |
| Std Dev: | 78.70 | 30.23 | 143.73 | 113.96 | 116.51 |

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|---|---|---|
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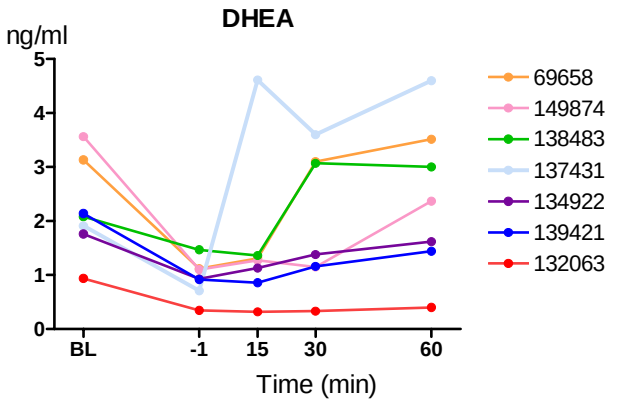
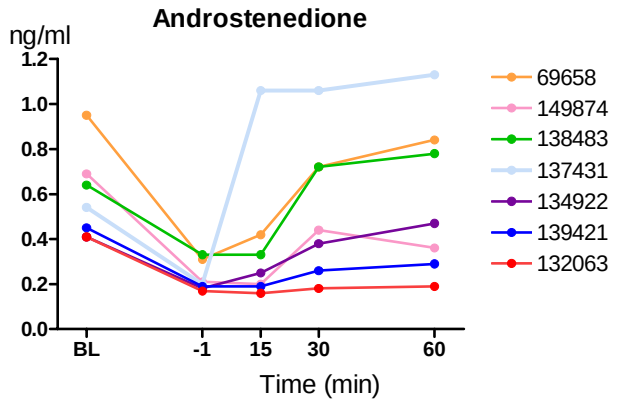
| Std Dev: | 14.78 | 49.47 |




| | | | | | |
|---|---|---|---|---|---|
| Mean: | 2.22 | 0.94 | 1.55 | 1.97 | 2.42 |
| Std Dev: | 0.87 | 0.35 | 1.40 | 1.26 | 1.41 |




| | | | | | |
|---|---|---|---|---|---|
| Mean: | 0.59 | 0.23 | 0.37 | 0.54 | 0.58 |
| Std Dev: | 0.20 | 0.07 | 0.31 | 0.31 | 0.34 |

## Figure 1 (continued)

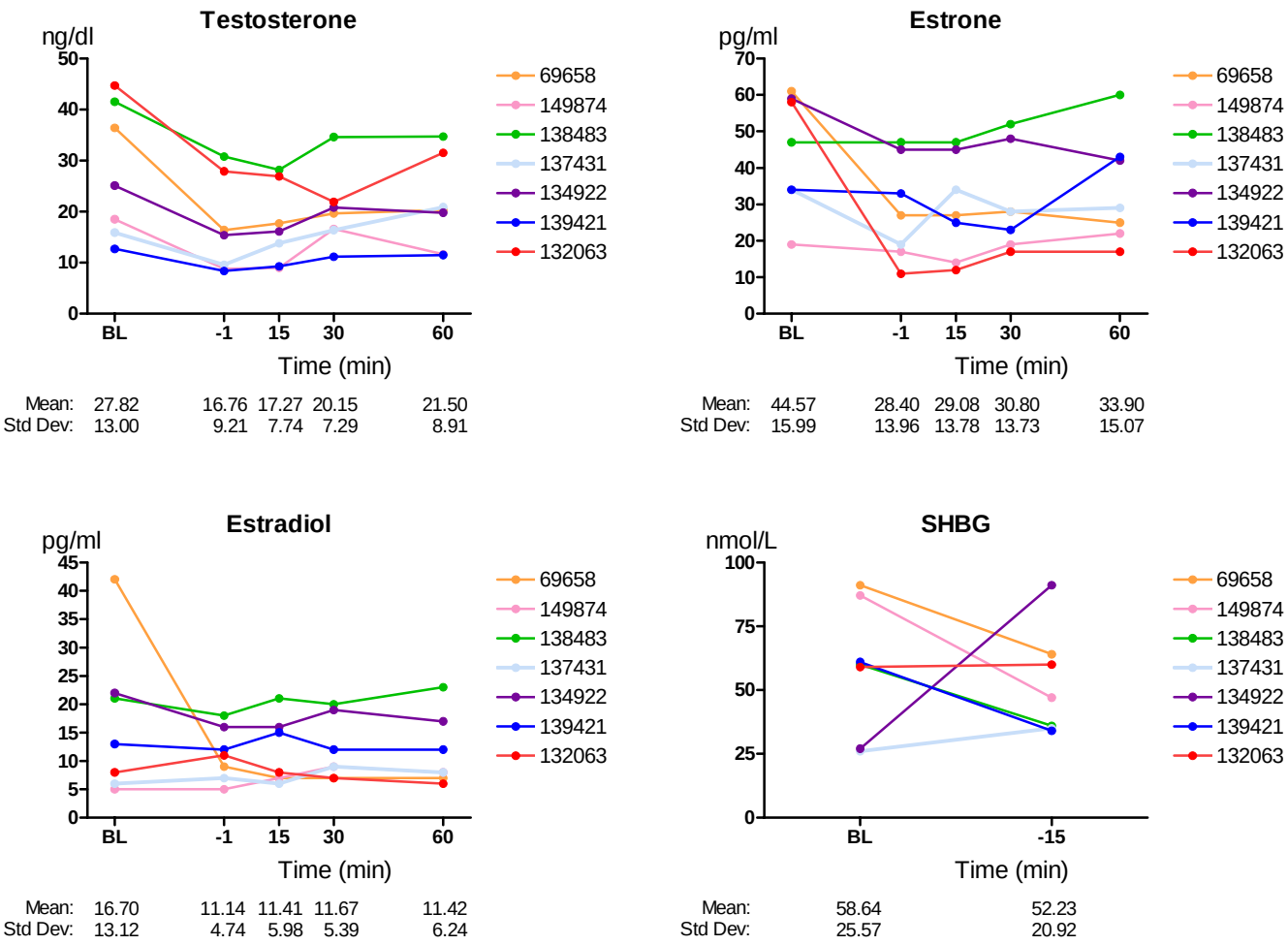
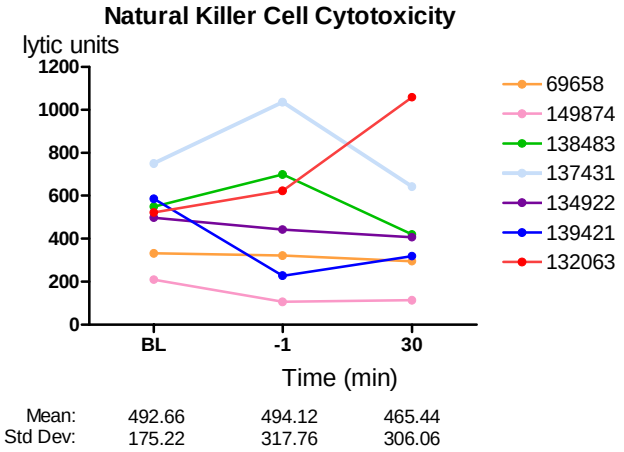


**Figure 2. Natural Killer Cell Cytotoxicity following Dexamathosone Suppression and ACTH Stimulation in Postmenopausal Women**



## Figure 3. Serum TNF-α, IL-6 and Leptin Concentrations in Postmenopausal Women